Clinical Significance of Atypical Glandular Cells in Cervical Papanicolaou Smears

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Objective: *To determine the prevalence and the rate of clinically significant lesions in women with atypical glandular cells in cervical Papanicolaou smears.*
Material and Method: *A retrospective study was performed from the cytologic database of Charoenkrung Pracharak Hospital. All cervical cytologic examinations with a diagnosis of atypical glandular cells (AGC) between January 2002 and December 2009 were identified. Medical records were reviewed to determine the clinical data. Cytologic and histologic follow-up was obtained to establish the presence of clinically significant lesions.*
Results: *One hundred eleven AGC Pap smears were identified from 47,347 Pap smears. The prevalence of AGC was 0.23% over the eight years of the period studied. Clinically significant lesions were diagnosed in 32.4% of the women, including invasive cancer in 18.3%. Women with AGC favor neoplasia were more likely to have clinically significant lesions (53.8%) than women with AGC not otherwise specified (20%, p = 0.003). The rate of clinically significant lesions in women aged 35 years or older (35.7%) was not statistically significant different from women younger than 35 years of age (20%, p = 0.356). All cases of invasive cancer were found in women aged 35 years or older. Cervical adenocarcinoma was the most common invasive cancer found in the present study.*
Conclusion: *Women with atypical glandular cells on Papanicolaou smears were correlated with significant risk for clinically significant lesions, including invasive cancer. Initial evaluation should include colposcopy, directed biopsy, and endocervical curettage. Women with risk factors for endometrial cancer should have an endometrial sampling.*

Keywords: *Atypical glandular cells, AGC, Papanicolaou smear, Bethesda System*

J Med Assoc Thai 2012; 95 (8): 975-82
Full text. e-Journal: *http://jmat.mat.or.th*

Cervical cancer is the second most common cancer in women worldwide. It remains a major cause of morbidity and mortality among women. In Thailand, cervical cancer is the second most common cancer in women with an age-standardized incidence rate of 18.1 per 100,000 women in 2002[1].The majority of cases are squamous cell carcinoma and 9.8-22.8% are adenocarcinoma[1]. Screenings have a significant impact on cervical cancer incidence. Incidences are declining in developed parts of the country with widespread screening programs. In 1988, the Bethesda System introduced the term atypical glandular cells of undetermined significance (AGUS) to describe endocervical or endometrial cells with atypia as more severe than that expected from a benign reactive change but lacking diagnostic features of invasive adenocarcinoma[2]. The qualifiers "favor reactive" and "favor neoplasia" were added to the category to help differentiate between benign reactive and neoplastic processes[3]. The finding of atypical glandular cells is important clinically because the percentage of cases associated with underlying high-grade lesions is higher than atypical squamous cells of undetermined significance (ASC-US). Either squamous or glandular high-grade lesion (cervical intraepithelial neoplasia 2, 3, adenocarcinoma in situ, or cancer) is seen in 9 to 38% of such cases[4]. The 2001 Bethesda System changed the terminology to atypical glandular cells (AGC) and eliminated the misleading term "favor reactive" subclassification[5,6]. Atypical glandular cells may arise from the endocervix, endometrium, ovary, fallopian tube, or any glandular epithelial source within the pelvis. The presence of atypical glandular cells may also be associated with underlying squamous lesions[4,7-10]. The present study was designed to

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estimate the rate of underlying clinically significant lesions in women with AGC Pap smears and a lack of known cervical or uterine disease. The authors also estimate the risk of underlying lesions based on the patient's age and AGC subclassification.

Material and Method

After approval by the Ethics Committee involving Human Subjects of the Bangkok Metropolitan Administration, the study sample was identified by a retrospective search at Charoenkrung Pracharak Hospital for cases of AGUS/AGC Pap smears between January 2002 and December 2009. Inclusion criteria were women who had AGUS or AGC cytology from conventional Pap smears and who underwent further investigation such as colposcopy, directed biopsy, endocervical curettage, endometrial sampling, fractional curettage, or a diagnostic excisional procedure. Exclusion criteria were women with known cervical or uterine disease likely accounting for the AGC Pap smear, women who had a total hysterectomy, women who lacked any follow-up data, or AGC with concurrent squamous intraepithelial lesions.

The demographic characteristics and Pap smear subclassification were recorded. Based on their descriptive modifier, AGC were categorized into one of these two groups, not otherwise specified (NOS), or favor neoplasia. Histologic findings were evaluated from the initial AGC Pap smear. Clinically significant lesions were the most severe pathologic finding and defined as a histologic result of cervical intraepithelial neoplasia (CIN 2, 3), adenocarcinoma in situ (AIS), atypical endometrial hyperplasia, or invasive carcinoma of cervix, or endometrium, or other genital organ. CIN 1 was documented but not listed as a clinically significant lesion.

Statistical analysis was performed using the Chi-squared test or Fisher's exact test with a value of $p < 0.05$ was considered statistically significant. Odds ratios (OR) with 95% confidence interval (95% CI) were used to evaluate the association between the various risk factors and the diagnosis of clinically significant lesions.

Results

During the eight-year study period, there were 111 Pap smears reported as AGUS/AGC out of 47,347 Pap smears performed. This resulted in a prevalence of 0.23%. Among these 111 women, 40 cases were excluded from the study sample due to the following reasons, 29 cases lacked any follow-up data, nine cases had concurrent AGC and high-grade squamous intraepithelial lesion (HSIL) at cytology, and two cases had total hysterectomies before the cytologic result of AGC. The remaining 71 subjects formed the final study sample. Nine women with concurrent AGC and HSIL were also searched for histologic diagnosis and were analyzed separately.

The mean age of the 71 women who had histologic results was 43 years. Five women (7%) were nulligravid, and 16 women (22%) were postmenopausal. The authors identified clinically significant lesions (CIN 2, 3, AIS or cancer) in 23 of the 71 women (32.4%) as presented in Table 1.

Glandular lesions accounted for 78.3% of the significant findings, and 21.7% were squamous lesions. Fifteen women (21%) were younger than 35 years old, and fifty-six (79%) were 35 years old or older. The rate of clinically significant lesions in women aged 35 years or older was 35.7%, and in women aged younger than 35 years it was 20%. The odds ratio of women aged 35 years or older having clinically significant lesions as compared to women aged younger than 35 years was 2.2 (95% CI 0.6-8.8, $p = 0.356$). The rate of glandular lesions in women aged 35 years or older was 28.6%, and in women aged younger than 35 years it was 13.3%. The odds ratio of women aged 35 years or older having glandular lesions as compared to women aged younger than 35 years was 2.6 (95% CI 0.5-12.9, $p = 0.324$). There was not a statistically significant difference. All cases of invasive cancer (10 cases of cervical adenocarcinoma, one case of cervical squamous cell carcinoma, and

Table 1. Histologic diagnosis of AGC Pap smear (n = 71)

Diagnosis	n (%)
Normal	28 (39.4)
Cervicitis	10 (14.1)
CIN 1	10 (14.1)
CIN 2, 3	4 (5.6)
Cervical squamous cell carcinoma	1 (1.4)
AIS	2 (2.8)
Cervical adenocarcinoma	10 (14.1)
Atypical endometrial hyperplasia	4 (5.6)
Endometrial adenocarcinoma	2 (2.8)
Total	71

CIN = cervical intraepithelial neoplasia; AIS = adenocarcinoma in situ

two cases of endometrial cancer) were identified in women aged 35 years or older as presented in Table 2. There were two cases of cervical adenocarcinoma in situ in women aged younger than 35 years. The authors found only one case of CIN 2, 3 in women aged younger than 35 years, and three cases of CIN 2, 3 in women aged 35 years or older. The odds ratio of women aged younger than 35 years having CIN 2, 3 as compared to women aged 35 years or older was 1.3 (95% CI 0.02-17.1, p = 1.00).

Based on AGC subclassification, the authors found that 45 women (63%) were diagnosed as AGC not otherwise specified (AGC-NOS), and 26 women (37%) were diagnosed as AGC favor neoplasia. Nine (20%) of the 45 women with AGC-NOS had clinically significant lesions. Fourteen (53.8%) of the 26 women with AGC favor neoplasia had clinically significant lesions as presented in Table 3. The rate of clinically significant lesions in women with AGC favor neoplasia was greater than the rate in women with AGC-NOS (OR 4.7, 95% CI 1.6-13.5, p = 0.003). The overall rate of invasive cancer was 18.3%. The rate of invasive cancer in the AGC favor neoplasia group was 34.6%, and, in the AGC-NOS group, it was 8.9%. The odds ratio of women with AGC favor neoplasia having invasive cancer as compared to AGC-NOS was 5.4 (95% CI 1.5-20.0, p = 0.007). Cervical adenocarcinoma predominated the invasive cancer diagnosed in the present study group. The rate of cervical adenocarcinoma was 30.8% in the AGC favor neoplasia group. That

Table 2. Histologic diagnosis of AGC Pap smears by age group (n = 71)

Diagnosis	Age < 35 years	Age ≥ 35 years
Normal	7 (46.6)	21 (37.5)
Cervicitis	1 (6.7)	9 (16.1)
CIN 1	4 (26.7)	6 (10.7)
CIN 2, 3	1 (6.7)	3 (5.4)
Cervical squamous cell carcinoma	0	1 (1.8)
AIS	2 (13.3)	0
Cervical adenocarcinoma	0	10 (17.8)
Atypical endometrial hyperplasia	0	4 (7.1)
Endometrial adenocarcinoma	0	2 (3.6)
Total	15	56

CIN = cervical intraepithelial neoplasia; AIS = adenocarcinoma in situ
Values are n (%)

Table 3. Histologic diagnosis of AGC Pap smears by subclassification (n = 71)

Diagnosis	Not otherwise specified	Favor neoplasia
Normal	19 (42.2)	9 (34.6)
Cervicitis	8 (17.8)	2 (7.7)
CIN 1	9 (20.0)	1 (3.8)
CIN 2, 3	3 (6.7)	1 (3.8)
Cervical squamous cell carcinoma	0	1 (3.8)
AIS	0	2 (7.7)
Cervical adenocarcinoma	2 (4.4)	8 (30.8)
Atypical endometrial hyperplasia	2 (4.4)	2 (7.7)
Endometrial adenocarcinoma	2 (4.4)	0
Total	45	26

CIN = cervical intraepithelial neoplasia; AIS = adenocarcinoma in situ
Values are n (%)

was higher than the rate in the AGC-NOS group (4.4%, OR 9.6, 95% CI 1.6-97.5, p = 0.002).

Nine women had concurrent AGC and HSIL on Pap smears during the study period. Clinically significant lesions were identified in six cases, resulting in a rate of disease of 66.7%. The diagnosis in this group included three cases of CIN 3 and one case each of squamous cell carcinoma, cervical adenosquamous cell carcinoma, and CIN 3 with AIS. The odds ratio of women with concurrent AGC and HSIL having a disease as compared to women with AGC alone was 4.2 (95% CI 0.9-18.2, p = 0.065). There was not a statistically significant difference.

Discussion

The prevalence of AGC in the present study was 0.23%. That was similar to the previous studies (0.1-0.4%)[8-15]. The finding of an AGC Pap smear is frequently associated with underlying clinically significant lesions, including preinvasive and invasive cancer of the cervix, endometrium or ovary. Many studies have reported that 14-56% of women with AGC Pap smears have clinically significant lesions (CIN 2, 3, AIS, or cancer), and 4-22% have invasive cancer[8-10,13-16,19]. The rate of clinically significant lesions in the present study was 32.4%, and the rate of invasive cancer was 18.3%. The findings of the present study and the previous studies of women with AGUS/AGC are respectively presented in Table 4. The authors found that the rate of disease in women aged 35 years or older was more than the rate in women aged younger than 35 years. However, there was not a statistically significant difference. There were only three cases of clinically significant lesions in the group of women aged younger than 35 years. All of these three cases were preinvasive lesions including one case of CIN 3 and two cases of AIS. In women aged 35 years or older, the authors found that all cases of invasive cancer were in this age group which included ten cases of cervical adenocarcinoma, one case of cervical squamous cell carcinoma and two cases of endometrial adenocarcinoma. The present study showed that the patient's age is not a significant factor in predicting underlying lesions. The two cases of endometrial adenocarcinoma that were found in the women aged 35 years or older support the recommendation that women with AGC in this age group should be evaluated with endometrial sampling.

The AGC subclassification was used in predicting the risk of clinically significant lesions. Based on the 2001 Bethesda System, the AGC was classified into atypical glandular cells, either endocervical, endometrial, or glandular cells not otherwise specified (AGC-NOS); atypical glandular cells, either endocervical or glandular cells favor neoplasia (AGC "favor neoplasia"). Endocervical adenocarcinoma in situ (AIS) was a separate category. Various studies from individual centers have reported higher risks for disease among women with AGC favor neoplasia than among women with AGC-NOS. Biopsy confirmed clinically significant lesions have been found in 29-90% of women with AGC favor neoplasia compared to 9-43% of women with AGC-NOS[9,13,16,18]. In the present study, the authors found that women with AGC favor neoplasia were also at a greater risk for disease than women with AGC-NOS. The rate of

Table 4. Prevalence and rates of clinically significant lesion in studies of women with AGUS/AGC Pap smears

Study	Prevalence (%)	AGUS/AGC Pap smears with histologic evaluation	Rates of clinically significant lesions	Invasive cancer
Nasuti et al. (2002)	0.2	112	38 (34.0)	7 (6.2)
Tam et al. (2003)	NA	138	43 (31.0)	20 (14.5)
Chan et al. (2003)	0.4	72	31 (43.0)	10 (13.9)
Sharpless et al. (2005)	0.3	308	42 (14.0)	13 (4.2)
Daniel et al. (2005)	0.057	325	183 (56.3)	65 (20.0)
De Simone et al. (2006)	0.15	82	31 (38.0)	14 (17.0)
Kumar et al. (2007)	0.3	41	21 (51.0)	9 (22.0)
Zhao et al. (2009)	0.41	662	101 (15.3)	44 (6.6)
Present study	0.23	71	23 (32.4)	13 (18.3)

AGUS = atypical glandular cells of undetermined significance; AGC = atypical glandular cells; NA = not available
Values are n (%)

clinically significant lesions in the AGC favor neoplasia group was 53.8%, which was significantly higher than that in the AGC-NOS group (20%, OR 4.7, 95% CI 1.6-13.5, p = 0.003). The rate of invasive cancer was also higher in the AGC favor neoplasia group (34.6%) as compared to the AGC-NOS group (8.9%, OR 5.4, 95% CI 1.5-20.0, p = 0.007). This finding suggested that AGC subclassification is an important prognostic factor for predicting the risk of clinically significant lesions. The majority of the invasive cancer in the present study was cervical adenocarcinoma. The authors have not found that cervical intraepithelial neoplasia was the common clinically significant lesion identified in women with AGC as previous studies reported[7-10,12,19]. All cases of cervical adenocarcinoma found in the present study were in women age 35 years or older with a mean age of 46.5 years (range, 35-69 years). There were two cases of AIS in women aged younger than 35 years. Adenocarcinoma in situ was the recognizable precursor of cervical adenocarcinoma. Women diagnosed with AIS have an average age of 13 years younger than those with adenocarcinoma[20]. There is ample time for screening and early detection of the preinvasive glandular lesions. The incidence and mortality rate of cervical cancer have declined in developed countries since the implementation of cervical cytologic screening programs[21]. Cytologic screening is less effective at detecting adenocarcinoma and its precursor than detecting squamous cell carcinoma[22]. The decrease of the incidences is seen almost exclusively in squamous cell carcinoma. High false-negative rates for the detection of AIS have been well documented[23,24]. Poor detection rates may be due to sampling or screening/diagnostic errors[25,26]. The sampling error for AIS may be caused by distribution of the lesions within glands rather than at the surface. It may be due to the greater difficulty in sampling for glandular lesions that often arise high in the endocervical canal. Devices designed to improve sampling of the transformation zone such as the endocervical brush have been introduced. The screening or diagnostic error was defined as the smears with high-grade epithelial abnormality that was not diagnosed initially but a later review demonstrated possible or definite high-grade epithelial abnormality. Schoolland et al studied the sensitivity of detecting AIS by cervical smear; they reported low screening and diagnostic error rates in their laboratories[25].

The classification of atypical glandular cells of undetermined significance (AGUS) was introduced by the Bethesda System in 1988. The category was further subclassified as favoring a benign reactive or neoplastic process. In 2001, the term AGUS was renamed atypical glandular cells (AGC) to avoid confusion with atypical squamous cells of undetermined significance (ASC-US). Compared with ASC-US Pap smears, women with AGC have higher rates of clinically significant lesions. The qualifier "favor reactive" was considered misleading and it has been eliminated.

The authors found that women with concurrent AGC and HSIL have higher rates of clinically significant lesions (66.7%) compared to women with AGC alone (32.4%), but there was not a statistically significant difference (OR 4.2, 95% CI 0.9-18.2, p = 0.065). The majority of the lesions that were found in women with concurrent AGC and HSIL were CIN 3.

The present study is limited by the retrospective design and a small sample size. The rarity of AGC Pap smears limited the number of available cases for study. Some women were eliminated because of a failure to follow-up or a lack of clinical evaluation. The authors have not found that CIN is the common form of neoplasia identified in women with AGC. This may be caused by the differences in the study population and the institutional practice in reporting cytologic results. The cytomorphologic criteria and interobserver variability in the interpretation of AGC Pap smears are the common contributing factors[28,29]. The interpretation of squamous intraepithelial lesions involving endocervical glands forming neoplastic glandular lesions on Pap smears was documented in the literature[8,10,17]. Many cases of glandular lesions were also recognized in the course of the evaluation of women with abnormal squamous cytology.

The purpose of the present study was to determine the rate of clinically significant lesions in women who present with AGC Pap smears. The present findings demonstrate that a substantial percentage of AGC is associated with underlying high-grade lesions. The rate of clinically significant lesions varies with AGC subclassification; AGC favor neoplasia has a higher rate of high-grade lesions. The patient's age was not a significant factor for predicting underlying high-grade lesions. The initial evaluation for women with all subclassifications of AGC should include colposcopy, directed biopsy, and endocervical curettage. Endometrial sampling is recommended in women aged 35 years or older. Endometrial sampling is also recommended in women aged younger than 35 years with risk factors for endometrial cancer. If the

neoplastic lesion is not identified during the initial work up, it is recommended that women with AGC favor neoplasia should undergo a diagnostic excisional procedure[4,6]. Lack of adherence to recommended guidelines may account for an increased risk of invasive cancer caused by late-stage diagnosis[27].

Potential conflicts of interest

None.

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ความสำคัญทางคลินิกในสตรีที่มีผลการตรวจคัดกรองเซลล์วิทยามะเร็งปากมดลูกชนิด atypical glandular cells

สงวน โล่ห์จินดารัตน์, จิรพร เหลืองเมตตากุล, สุภลาภ พวงสอาด

วัตถุประสงค์: เพื่อหาความชุกของการตรวจคัดกรองเซลล์วิทยามะเร็งปากมดลูกชนิด atypical glandular cells (AGC) และศึกษาความสัมพันธ์ระหว่างผลการตรวจคัดกรองเซลล์วิทยามะเร็งปากมดลูกชนิด atypical glandular cells กับอัตราการตรวจพบรอยโรคที่มีความสำคัญทางคลินิกจากผลการตรวจทางพยาธิวิทยา

วัสดุและวิธีการ: ทำการศึกษาย้อนหลังโดยรวบรวมประวัติผู้ป่วยจากสตรีที่มีผลการตรวจคัดกรองเซลล์วิทยามะเร็งปากมดลูกมีผลเป็น atypical glandular cells ที่กลุ่มงานสูตินรีเวชกรรม โรงพยาบาลเจริญกรุงประชารักษ์ สำนักการแพทย์ กรุงเทพมหานคร ระหว่างเดือนมกราคม พ.ศ. 2545 ถึง ธันวาคม พ.ศ. 2552 ทำการรวบรวมข้อมูลพื้นฐานและผลการตรวจทางพยาธิวิทยาจากผลการตรวจวินิจฉัยเพิ่มเติมว่า มีรอยโรคที่มีความสำคัญทางคลินิกหรือไม่ ทำการวิเคราะห์หาอัตราการตรวจพบรอยโรคที่มีความสำคัญทางคลินิกและปัจจัยที่มีผลต่อการตรวจพบรอยโรคที่มีความสำคัญทางคลินิก

ผลการศึกษา: ในช่วงเวลาที่ทำการศึกษาพบสตรีที่มีผลการตรวจคัดกรองเซลล์วิทยามะเร็งปากมดลูกชนิด atypical glandular cells จำนวน 111 ราย จากการตรวจทั้งหมด 47,347 ครั้ง พบความชุกของการตรวจพบ atypical glandular cells ร้อยละ 0.23 ในสตรีที่รับการตรวจวินิจฉัยเพิ่มเติม พบอัตราการตรวจพบรอยโรคที่มีความสำคัญทางคลินิกร้อยละ 32.4 รวมถึงอัตราการตรวจพบมะเร็งระยะลุกลามร้อยละ 18.3 สตรีที่มีผลการตรวจคัดกรองเซลล์วิทยามะเร็งปากมดลูกชนิด AGC ที่มีส่วนขยายเป็น favor neoplasia มีอัตราการตรวจพบรอยโรคที่มีความสำคัญทางคลินิกร้อยละ 53.8 ซึ่งมากกว่าอัตราการตรวจพบรอยโรคที่มีความสำคัญทางคลินิกในกลุ่มสตรีที่มีส่วนขยายเป็น not otherwise specified อย่างมีนัยสำคัญทางสถิติ (ร้อยละ 20, p = 0.003) สตรีที่มีผลการตรวจคัดกรองเซลล์วิทยามะเร็งปากมดลูก ชนิด AGC ที่มีอายุ 35 ปีขึ้นไป มีอัตราการตรวจพบรอยโรคที่มีความสำคัญทางคลินิกร้อยละ 35.7 ซึ่งไม่แตกต่างจากอัตราการตรวจพบรอยโรคที่มีความสำคัญทางคลินิกในกลุ่มสตรีที่มีอายุน้อยกว่า 35 ปี อย่างมีนัยสำคัญทางสถิติ (ร้อยละ 20, p = 0.356) สตรีที่มีผลการตรวจวินิจฉัยเพิ่มเติมเป็นมะเร็งระยะลุกลามทุกรายมีอายุ 35 ปีขึ้นไป มะเร็งระยะลุกลามที่พบบ่อยที่สุดในการศึกษานี้ คือ cervical adenocarcinoma

สรุป: สตรีที่มีผลการตรวจคัดกรองเซลล์วิทยามะเร็งปากมดลูกชนิด atypical glandular cells สามารถตรวจพบรอยโรคที่มีความสำคัญทางคลินิกรวมทั้งมะเร็งระยะลุกลามในอัตราสูง ดังนั้นสตรีกลุ่มนี้จึงสมควรได้รับการตรวจวินิจฉัยเพิ่มเติม ได้แก่ การตรวจปากมดลูกด้วยกล้องส่องปากมดลูก การตัดชิ้นเนื้อปากมดลูกเพื่อส่งตรวจทางพยาธิวิทยา การขูดเนื้อเยื่อบุคอมดลูกเพื่อส่งตรวจทางพยาธิวิทยา สตรีที่มีความเสี่ยงต่อภาวะมะเร็งเยื่อบุโพรงมดลูกควรได้รับการเก็บเนื้อเยื่อบุโพรงมดลูกเพื่อส่งตรวจทางพยาธิวิทยา